EMBOLIZATION OF ARTERIOVENOUS FISTULAS WITH MICROSPHERES

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Embolization of Arteriovenous Fistulas with Microspheres

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Dedication

To W. W. L. Glenn, M.D.

For his kindness, generosity,
and guidance in this research,
and his personal effort to help
me to benefit by his experience.

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"No lesion illustrates so well as arteriovenous aneurysm how borderless are the fields of medicine and science."

Sir William Osler (27)

Part I. Review of Literature

INTRODUCTION

Abnormal communications between arteries and veins are usually divided into two groups: acquired and congenital (47). The acquired type usually follows trauma, such as a knife or bullet wound, and is characterized by a single arteriovenous communication. Congenital arteriovenous fistulas are present from birth, and characteristically are composed of multiple minute but direct channels between artery and vein. To these two classical groups should be added a third--the therapeutic arteriovenous fistula that is created by the surgeon to augment bone growth in cases of retarded bone growth (30).

Only the congenital types of arteriovenous fistula are dealt with here. Flynn has subdivided the congenital fistulas into three types based on number of communications, extent of lesion, and method of treatment (11). Type I consists of from one to eight congenital arteriovenous communications. These can be successfully treated by individual ligation. Type II consists of extensive congenital minute arteriovenous fistulas that involve an entire extremity with multiple, unidentifiable communications, for which there is at present no treatment other than amputation, when necessary. Type III consists of localized minute congenital arteriovenous fistulas that can be treated by complete excision together with ligation of the proximal arterial supply.

It is with the type II fistula that this study is primarily concerned. As noted above, at present the only treatment of this lesion is amputation, which is a therapeutic defeat for the surgeon. Flynn comments that in type II "...It is our regrettable experience that attempts at curative surgery in the group are fruitless. The proper manner for eradicating this type of lesion is not known at the present time; however, the condition certainly warrants every continued laboratory and clinical effort and thought (11)."

Over the years many names have been given to lesions that have been subsequently recognized as congenital arteriovenous fistulas. Robertson (51) has collected the following list of synonyms: arteriovenous aneurysm, anastomosis or fistula; cirsoid or racemose aneurysm; aneurysmal varix; cavernous, pulsating, plexiform, arterial or venous hemangioma; angiosarcoma; phlebarteriectasis; phlebectasis; hemangioectatic hypertrophy; hemihypertrophy; and generalized angiomatosis.

These lesions are slightly more common in males, and are most commonly found in the head and neck, and next most commonly in the extremities (60). These lesions have always been thought to be of infrequent clinical occurrence, and as late as 1930, Lewis (38) could find only 24 reported cases in the literature. A recent report estimates that there are still less than 250 cases reported (43) and a series from a large general hospital reported an incidence of one case per 10,000 admissions (57).

The physical findings in congenital arteriovenous fistulas have been enumerated by Coursley (8) in decreasing order of their clinical frequency: enlargement of involved limbs, increased warmth of skin, presence of varices, a bruit, vascular mass, port wine stain, stasis skin changes, and ulceration. Unceration, however, is a frequent presenting symptom, according to Robertson (51). He also notes that pain due to ischemia, hemorrhage, superficial venous dilatation, or a pulsatile swelling may be the reason for consulting a physician. In addition to those clinical findings listed above, Keeley (31) adds that a thrill may be felt, or venous pulsations seen, and arterial insufficiency may give rise to claudication or even gangrene. In addition, there may be edema due to increased venous pressure distal to the lesion, and increased oxygen saturation of venous blood.

In this country cases of congenital arteriovenous fistula have usually been designated as the Klippel-Trenaunay syndrome (32) or alternately as the Parkes-Weber syndrome (46). Recently, Lindenauer (40) has reviewed the original descriptions of these authors and has proposed that the Klippel-Trenaunay syndrome be restricted to those cases of varices, hemihypertrophy and hemangioma without evidence of arteriovenous fistula. When such a fistula is present with these symptoms, he suggests the Parkes-Weber designation be used.

Systemic clinical signs of arteriovenous fistulae include increases in pulse rate, heart size, blood volume and cardiac output, and decreases in diastolic pressure and

The [illegible] findings [illegible] ([illegible]) [illegible] have been demonstrated by [illegible] of their typical [illegible] involvement of [illegible] basilar [illegible] hypertension [illegible] one, according to [illegible] due to ischemia [illegible] or a [illegible] physician). In addition [illegible] ([illegible]) [illegible] pulsations [illegible] and arterial [illegible]

In [illegible] many [illegible] of [illegible] the [illegible]

Recent [illegible]

circulation time (31). Despite these changes, obvious cardiac failure in patients with congenital arteriovenous fistula is rare, being present in only two of 185 patients reported by Schumacker (56).

HISTORY

Though all authors agree that William Hunter was the first to describe the clinical syndrome of acquired arteriovenous fistula in 1757 (28), there is much disagreement over who described the first congenital fistula. Reinhoff (50) gives credit to Hewitt (17) for reporting the first case in 1867, though Lewis (38) cites Lettenneur as describing the first case in 1859 (35). Robertson (51) has found a case reported one year before that, in 1858 (1), while Callander, in a comprehensive review article (7) gives credit to Busche in 1827 (6). Regardless of who reported the first case, reports in the literature were few until the 1920's, and very little clinical or laboratory investigation was undertaken. From this time on, several investigators began to study the lesion, notably Reid (49) and Holman (19, 20, 21). It has been only since this time that the different types of arteriovenous fistula have been commonly recognized, and to many physicians, it is still a curiosity.

EMBRYOLOGY

In order to study the pathogenesis of congenital arteriovenous fistula, it is necessary to study the development of

arteries and veins embryologically. Wollard (62) has studied the development of vessels in the forelimb of the pig, and reports three stages of development. The first is the stage of the capillary net, without larger channels or pulsating blood. The second stage is characterized by enlarged tubes which coalesce and fuse, called by him the retiform stage. The third stage is characterized by definite arterial and venous channels, with an interposed capillary network. Florence Sabin has made many important observations on the embryology of blood vessels. She has demonstrated that both arteries and veins develop from a common capillary plexus and has made the important observation that during this development the direction of flow through a capillary plexus may change ------ --early arteries may change later to veins and veins to arteries (53). These observations form the basis of development of a congenital arteriovenous fistula. In a personal communication to W. S. Halsted, Sabin states "...the underlying principle that arteries and veins develop out of a common capillary plexus forms the basis for the persistence of direct connections between them (15)." Reinhoff has also done experimental work demonstrating a uniform capillary network that is "...rich in anastomoses, offering ample opportunity for the formation of an arteriovenous fistula (50)." He also believes that irritation causes the persistence of these arteriovenous communications but does not state the nature of this irritation. Reinhoff further cites an experiment of Sabin's, in which the insertion of a capillary pipette into a chick embryo created an

arteriovenous fistula between the omphalomesenteric artery and vein. In this A-V fistula, the amount of blood transfer increased from an occasional corpuscle passing through the arteriovenous communication to almost half the blood in the artery passing through it during a time span of one and a half hours (18).

PHYSIOLOGY

Anatomically, there are several types of arteriovenous fistulas as described above. Physiologically, however, no distinction need be made according to anatomical types, for Pemberton and Saint (47) have presented instructive data indicating that congenital fistulae resemble the acquired lesions physiologically in every respect. Holman has made many important studies of arteriovenous fistulas and has enumerated the gross patho-physiological alterations that occur in such lesions (18). He lists a fall in blood pressure, increased heart rate, increased blood volume, and increased cardiac output as characteristic of fistula. There is also the bradycardiac phenomenon of Branham (4), in which occlusion of the artery proximal to the fistula results in a slowing of the pulse rate.

The fall in blood pressure upon opening an arteriovenous fistula is both systolic and diastolic. Over time, blood volume increases, and systolic pressure is restored, but diastolic pressure remains permanently lowered. The venous pressure

in the region of the fistula is increased, but in the absence of heart failure, central venous pressure is not increased. Due to the Bainbridge reflex (20), there is an increased cardiac output, as described by Harrison (16). Frank (12) has quantatively measured cardiac output with fistulas of various sizes. If up to 20% of the cardiac output flowed through the fistula, cardiac output increased the full amount of the fistula flow, and vasoconstriction occurred, which prevented a fall in mean arterial pressure. But in larger fistulas in which 60% of the cardiac output was shunted, cardiac output and vasoconstriction were inadequate to maintain the blood pressure. This author believes cardiac output lagged due to inadequate venous return.

Holman has also shown that excision of an arteriovenous fistula results in regression of the rise in heart rate and blood volume that he lists as cardinal signs of fistula (18). He also has observed that the slowing of heart rate with the closure of a fistula is vagally mediated, since the slowing can be abolished with atropine (26).

The altered physiology of blood flow in arteriovenous fistula results in local and systemic changes in the heart and vessels. One of the first observations on fistulas was that the proximal artery was usually dilated. Holman (22) was the first to describe the occasional distal dilatation of the artery, which he found is due to a most interesting alteration in flow. He demonstrated that if the fistula is capable of transmitting more blood than the proximal artery is capable of

delivering, collateral channels form to the distal artery with resulting retrograde flow of blood in this segment and consequent dilatation. This distal dilatation is due, he believes, to the mechanical factor of increased blood flow. There is increased blood volume, as pointed out above, and this results in cardiac dilatation and hypertrophy as well as regional engorgement of the vessels at the site of the fistula.

The oxygen content of the vein proximal to the arteriovenous fistula is higher than the normal venous blood (5). The rapid flow of blood from artery to vein also produces unique pressure relationships. Freeman (13) found the mean pressure within a fistula to be 40 mm. Hg. with a range of 30 to 70 mm. Hg. with pulsatile blood flow. With constriction of the afferent artery, the pressure fell to 10 mm. Hg. Holman (23) cites an interesting case in which the distal artery and vein were both ligated, and a hole inadvertently punctured in the fistula, with an immediate inrush of air signifying a constant negative pressure. This he attributed to a sort of Venturi effect of the rapid flow of blood from the artery to vein.

A fascinating accompaniment to arteriovenous fistula is the marked development of collateral circulation. Reid has stated that arteriovenous fistula is the most powerful stimulus to collateral circulation known (49), and as Holman has so aptly put it, "All avenues of approach to the fistula open up to appease, as it were, the thirst of the fistula (18)." There

are, however, several viewpoints as to why this collateral circulation develops. Holman and Taylor (23) have recognized two basic anatomical conditions that must be satisfied: the size of the fistula must be larger than the proximal artery, and a widely open distal artery with ready access to the low pressure area through the fistula must be present. But exactly what the stimulus for collateral development is under these circumstances is a matter of argument. Thoma has made the suggestion (58) that collaterals develop around a fistula because blood flow through these vessels is increased. Lewis (40) points out, however, that with the increase of flow already due to fistula a further increase in flow is unreasonable. Lewis himself postulates that local production of a chemical stimulant from ischemic tissue as a stimulus to collateral circulation. And Pennoyer (48) believes in a similar humoral basis for collateral development. He believes that anoxemia with buildup of the end products of metabolism is the most important stimulus. Reid (49) simply states that collaterals develop to meet the demands of tissue deprived of its blood supply. These last three theories depend uponischemic tissues for the development of collateral circulation, but a case observed by Holman, in which the distal ischemic tissue had been amputated, also produced a profuse collateral circulation. Holman concluded "...that ischemic tissues are unnecessary for the development of abundant collateral circulation (24)."

The effect of sympathectomy on the development of collateral

circulation in arteriovenous fistula has been studied by several groups. Mulvihill and Harvey (45) demonstrated the use of sympathectomy to allow collateral vessels to reach their maximum dilatation, and Robertson (52) quantitatively measured the blood flow in the extremities of dogs to measure collateral circulation. This study and others (44, 49) agree that sympathectomy is of value in increasing the size and number of collateral channels around an arteriovenous fistula.

Experimental studies to elucidate further the physiology of arteriovenous fistulas have contributed much to the understanding of these lesions. Holman has discovered that the collateral circulation that usually develops around a fistula can be greatly increased if the proximal artery is ligated after flow is well established (25). He also found that conversely, ligation of the distal artery prevents collateral circulation (22). Other features that may accompany the increased collateral vascularity include hemihypertrophy of the extremity, due to overnutrition of the epiphysis (30), and changes in skin temperature at the site of an distal to the lesion. The skin temperature and oxygen saturation of venous blood was quantitatively studied by Ingebrigtsen (29). The immediate effect of opening a femoral arteriovenous fistula was found to be a lowering of the temperature distal to the fistula and a decrease in the oxygen saturation of the saphenous vein blood. After a few weeks the temperature rose distal to the fistula, and oxygen content in the saphenous vein

rose. These changes are both due to development of adequate collateral circulation.

Several other physiological methods of studying arteriovenous fistulas have been used. Watkin and Hames (61) used plethysmography to study blood flow in the distal extremity before and after creation of an arteriovenous fistula and also after repair of the lesion. They found that the presence of the fistula reduced distal flow, but that this was restored after surgical repair. Bertelsen studied flow by the same method in congenital peripheral lesions (2). This study reports a marked increase in total flow in the extremity after exercise, though they did not measure flow distal to the lesion as did Watkin and James. Sir Thomas Lewis has used the calorimeter (39) to measure the heat given off by fistulous and normal extremities, and found heat given off much greater in the fistulous than in the normal extremity.

PATHOLOGY

The pathology of congenital peripheral arteriovenous fistulas can be considered under gross and microscopic categories. Grossly, there may be enlargement of the limb, both in circumference and in length (hemihypertrophy), the presence of varicose veins, stasis ulcers, and skin changes (8). The underlying pathological lesion, however, is microscopic, for it consists of multiple small arteriovenous anastomoses (33). The size of these small arteriovenous communications is given by Lawton as measuring from 0.05 to 0.50 mm. in diameter (33),

but by Bosher as measuring from 0.075 to 1.20 mm. in outside diameter (3). Regardless of the size variation in the vessels, it is important to note that the total cross-sectional area of the shunts may be greater in a multiple congenital fistula than in a single, large, acquired fistula (33). Lawton has given an excellent brief description of the altered conditions resulting in the gross pathologic features of fistula (33):

> Arteriovenous shunts at the capillary level do not nourish tissue. They are parasitic upon the circulation. Although the involved extremity has a great volume of blood coursing through it, tissue requirements may be barely sustained. The major portion of blood is shunted around the functional capillary bed because of the lower resistance to flow in the fistula.

There are also microscopic lesions that are present in the small arteriovenous communications. The internal elastic membrane is fragmented, frayed, and sometimes destroyed. The intima contains increased amounts of subendothelial tissue, which is never focal like a plaque but which has been identified as fibroblastic tissue. Also, a thickening of the adventitia is present in some cases (3).

DIAGNOSIS

Any of the clinical features of arteriovenous fistula as listed above may be used as a basis for diagnosis, but Leonard and Vassos (34) list a useful series of diagnostic signs: trophic changes, bruit, thrill, cardiac enlargement, increase in surface temperature and oxygen saturation, limb hypertrophy, and the bradycardiac phenomenon. Specific procedures used to diagnose congenital arteriovenous fistula include

all those used to study the lesion, but notably include auscultation, roentgenography, and oxygen saturation studies. Edwards and Levine (10) describe the characteristic murmur of arteriovenous fistula, and state that in their experience, no fistula has been demonstrated by angiography that cannot be demonstrated by a murmur on auscultation. However, they point out that no murmur does not necessarily mean no fistula. The roentgenology of arteriovenous fistula has been studied by several authors (55, 59) with the result that small arteriovenous fistulas may not be apparent and much of what is seen on conventional angiograms represents veins, not arteriovenous communications. Possible diagnosis of arteriovenous fistula by the oxygen saturation of venous blood (5) has been referred to above, but this method is considered unreliable by others, since high oxygen saturations may be obtained from venous blood of volunteers if there is vasodilatation (51).

TREATMENT

In the classification of congenital arteriovenous fistulas proposed by Flynn (11) and referred to above (p. 1) the treatment of choice is simple ligation when possible, as in their type I. The next most desirable treatment is surgical extirpation and, if necessary, proximal arterial ligation for the small localized lesion, which this author classifies as type III. It is the type II, the extensive multiple congenital fistula, for which there is, at present, no treatment other than amputation (11). Amputation is always a drastic measure

and many proposals have been made to postpone or delay this admission of failure.

Malan (41) has outlined the two principal aims in the treatment of congenital arteriovenous fistulas: the first, to re-establish anatomical and functional normality; the second, to neutralize the local and systemic hemodynamic damage. Esthetic and orthopedic treatment are of secondary importance. In the actual surgical treatment of the congenital lesions, Holman has emphasized that where there are multiple communications between artery and vein a cure can be effected only by eliminating all the communications (18). If this is not done, numerous channels will reform the fistula. In fact, another author states that in this lesion, extensive removal is based on the same principles as those governing malignancy (41). In any case, most authorities agree that treatment should be individualized. Radical surgical attempts to extirpate the massive type II fistula are now not advised by most authors; in fact, the most recent work on this problem concludes with a plan for conservative treatment (57).

In lesions for which there is no acceptable treatment, a number of experimental procedures are attempted with hopes for good results. One treatment that would naturally occur to most surgeons is ligation of the proximal artery. Holman (26) has taught for years that this is absolutely contraindicated in large congenital fistulas, because gangrene of the distal extremity will inevitably occur. Other ligation procedures, such as ligation of both proximal artery and vein

or quadruple ligation of artery and vein with excision, are rarely possible in type II fistulas. The injection of sclerosing solution has been tried, with good results reported in the few cases treated (54). The use of a slowly constricting arterial band around a proximal artery has been used in a few cases (57), but it is emphasized that this does not cure the lesion. Clearly, other methods of treatment should be sought.

Part II. Experimental

INTRODUCTION

Peripheral congenital arteriovenous fistula is at the present time a therapeutic enigma. Many types of treatments have been tried, but none has been completely successful. This study is an attempt to evaluate the treatment of a model of congenital peripheral arteriovenous fistula by injection (embolization) of microspheres to the fistulous area.

The treatment of arteriovenous fistula by embolization has been suggested and used in a few instances previously. Gerbode and Holman (14) report treatment of a congenital arteriovenous fistula between the internal maxillary artery and pterygoid plexus by embolizing muscle to the site of the fistula. This treatment was apparently successful, for on examination two and one-half months later only a faint bruit was heard where a loud one was heard before. Embolization of spherical particles has also been used to treat congenital cerebral arteriovenous fistulas. Luessenhop has used larger plastic spheres in the treatment of congenital arteriovenous fistulas in the brain, with apparent success (36, 37). McCaughan has treated one case of congenital arteriovenous fistula of the right cheek by injection of 150 mg. of microspheres of 150-450 microns in diameter with immediate success, for on examination after two months there was no pulsation, bruit, or murmur (42). An unfortunate complication of his case was the loss of sight in the right eye following treatment, apparently due to a

microsphere reaching the ophthalmic artery.

Despite the tragic complication in this case, the success of the method justifies its further study. Such study should be done in animals before further clinical attempts are tried. The major factor retarding such research at present is the lack of a suitable lesion in animals to study. McCaughan has remarked that "Unfortunately, no experimental congenital arteriovenous fistulas can be devised to test this method (42)".

MATERIALS AND METHODS

A surgically created model of congenital arteriovenous fistula, based on the work of Emile Holman (18), can be created in dogs. This experimental model of congenital arteriovenous fistula can be used to study the treatment of arteriovenous fistula by embolization with microspheres. Holman showed that if an arteriovenous fistula is created in the femoral vessels of a dog, and several weeks later the femoral artery is ligated proximally to the fistula, then in four to five months a remarkable collateral circulation develops from the arteries proximal to the ligature to the distal arteries.

This collateral circulation is composed of small tortuous arteries and is somewhat analagous to those found in congenital arteriovenous fistulas. The marked similarity between the surgically created lesion and congenital arteriovenous fistula can be seen by comparing the angiograms in Plate 1a and 1b. As far as we can determine, this lesion has not previously been

proposed as an experimental model of congenital arteriovenous fistula.

We have used this lesion to study the effects of embolization of small arteries with microspheres. An arteriovenous fistula was created in ten animals, and sometime after the ligation of the artery proximal to the fistula, microspheres were injected through a catheter passed into the femoral artery via the left carotid artery and aorta. Also, injection of microspheres was made in the extremities of eighteen normal dogs to determine the effect of the microspheres on the normal circulation. The blocking effect of the microspheres on the circulation was studied by angiography and in some cases, by blood flow studies and by determination of oxygen content of the arterial and venous blood. Studies were also carried out to determine whether microspheres entered the veins after injection into the arteries.

A. NORMAL ANIMALS

Mongrel dogs weighing nine to 20 kilograms (Table 1) were anesthetized with intravenous Nembutal anesthesia. A left carotid cutdown was performed, and a radiopaque catheter was passed under fluoroscopic control through the aorta into the femoral artery. With the catheter in the femoral artery ten ml. of Renovist was injected with a power syringe at 60 psi. and seven angiograms were taken at one per second with the Schonander apparatus. The radiation technique was usually 90 kv. and 4.5 mas. at 36 inches with a degrading filter. After the normal angiograms were obtained, doses of microspheres

varying from 250 to 2100 mg. of glass or steel were injected, the sizes of which varied from 28 to 1170 microns in diameter (Table 2). The microspheres were flushed in with ten ml. of saline containing 10 mg. of heparin, and the blocking effect of the microspheres on the circulation was determined by repeating the angiogram using the same technique as described above. The catheter was then removed, the carotid artery repaired with 6-0 arterial silk, and the skin incision was closed. The animal was given one million units of penicillin and 0.5 gram of streptomycin. A follow up angiogram was taken from 14 to 30 days later to determine the long-term effect of the microspheres.

Magnification angiograms of normal animals using the same operative and injection techniques were made, except that a Siemens Bi-Angulex tube with a 0.26 mm. focal spot was used as an x-ray source. Magnification with this equipment was approximately 2.5 diameters.

Blood flow rate studies made before and after injection of microspheres were performed using the Medicon Microflo K-2000 Electromagnetif Flowmeter. Flow rates were calibrated by matching base readings with flow rates measured at a later date from bilateral femoral artery cannulation in a dog.

B. FISTULA ANIMALS

Mongrel dogs weighing 16 to 23 kilograms (Table 1) were anesthetized with intravenous Nembutal anesthesia. The

right femoral area was shaved, and using sterile technique, this area was prepared and draped in the usual manner. A five cm. skin incision was made over the femoral artery, and the sartorius muscle retracted laterally. The femoral artery and vein were dissected free from the surrounding fascia for three cm. Small muscular branches were ligated if necessary. DeBakey clamps were applied across artery and vein proximally and distally, and the adventitia was stripped from the vessels. A short slit was made in each vessel with a number 11 blade, and the incision extended to two cm. with Pott's scissors. Stay sutures of 6-0 arterial silk were then tied at the ends of the incisions in the vessels, securing the apex of the incision in the artery to that of the vein. The posterior edges of the vessels were then sewn together using an over and over stitch. When completed, the posterior suture was tied to the distal stay suture, and the anterior edges were sutured, again using an over and over stitch. When completed, this was anchored to the proximal stay suture. When the DeBakey clamps were released, brisk hemorrhage always occurred, but this could always be stopped by compressing the fistula with firm pressure for ten minutes. The subcutaneous tissues were approximated with 2-0 chromic catgut and the skin incision with 4-0 interrupted silk.

Approximately three weeks later, the femoral artery was ligated just proximal to the arteriovenous fistula to produce an abundant collateral circulation. The right femoral

area was prepared and draped in the usual manner, and a skin incision made just proximal to the fistula. The fascia was spread until the fistula could be identified, and the proximal artery was identified and doubly ligated with 2-0 silk. The subcutaneous tissues were approximated with 3-0 chromic catgue and the skin incision closed with interrupted 3-0 silk sutures.

The animals were then allowed to develop collateral circulation over a period of four to five months. At the end of this time, catheterization and microsphere injections were made using exactly the same techniques as for the normal animals, except that a snare ligature was placed around the catheterized artery through an abdominal incision and was tightened just prior to the injection of dye through the catheter. Bucky, Schonander, and magnification angiograms were made in the same manner as for the normal animals. Blood flow rate studies were also performed in the same manner as above.

In several of the fistula animals, arterial and venous oxygen saturation studies were performed before and after microsphere injection to determine whether blocking some of the collateral arterial channels would decrease the oxygen saturation of the venous blood. The external iliac artery and vein were directly punctured through the abdominal incision to obtain the blood samples. The PO_2 and per cent saturation were determined by standard techniques using a

Beckman Blood Gas Analyzer.

C. MICROSPHERE TRAP EXPERIMENT

In order to determine whether or not injected microspheres passed from the arterial to the venous system, a polyethylene trap was inserted into the inferior vena cava of six animals (Plate 2). In one animal, used as a positive control, the microspheres were injected into the leg veins directly rather than into the arteries through a catheter. In other animals, the catheter was passed through the carotid artery to both femorals in the usual manner, and in these normal animals two grams of the smallest size microsphere used, 28-53 microns in diameter, was injected into each lower extremity. In the fistula animals, microspheres 590-840 microns in diameter were found most effective in blocking flow.

After the microspheres were injected, the inferior vena cava was clamped near each end of the microsphere trap, and a ligature placed proximally and distally to the clamps at each end of the trap. The trap was then removed by cutting the vessel between the ligatures, and the contents of the trap flushed with heparinized saline into filter paper. The contents were then examined grossly and by low power microscopy. The microspheres could be positively identified by their characteristic refractile appearance.

RESULTS AND DISCUSSION

A. NORMAL ANIMALS

If an angiogram of a normal dog extremity before injection of microspheres is compared to an angiogram after injection, definite obstruction to blood flow can be demonstrated (Plate 3a and 3b). Inspection of serial angiograms also demonstrates that the arterial phase persists longer after microspheres are injected, showing retardation of flow. Both of these effects could be consistently produced. The degree of blockage could be qualitatively related to the dose of microspheres injected. This parameter was quantitatively documented in the blood flow studies described below. The degree of blockage was also related to the number of smaller branches injected by specifically placing the catheter in the branch before injection.

The distribution of the obstruction produced by the microspheres (Plate 4) is dependent on two major factors. First, the more dependent vessels were more readily occluded, indicating that gravity is a factor. This is particularly true with the larger sized and the metallic microspheres. Second, the angle at which the smaller sized vessels branched from the larger one appeared to influence the course of the microspheres. The more acute this angle, the larger seemed to be the dose of microspheres received by the branch. In general, the most effective method of producing an obstruction was to inject small doses into each of many individually

cannulated branch arteries, positioning the limb so that the vessel was in a dependent position at the time of injection.

Several observations were made about the changes in the angiograms in the animals after injection of microspheres. Venous filling as shown on rapid sequence angiograms appears earlier in the injected animals than in the same animals before injection. This may occur because arteriovenous shunts that are normally closed open after the microspheres are injected, resulting in a short circuiting of blood around the block.

The distention of the arteries of the normal animals after injection of microspheres was consistently greater than before injection using identical volumes of radiopaque dye and injection pressures. This is probably due to the fact that the obstruction of the microspheres slows the arterial run off, thus holding back a larger volume of dye to increase distention in the arterial channels.

Whenever several doses of microspheres were injected into a normal extremity, obstruction to flow was produced in the vessels in the area of the tip of the catheter. On repeating the angiogram, vessels proximal to the tip that were not filled with dye before the injection of microspheres could now be visualized. The most effective technique for blocking the arterial tree was to begin distally and work proximally, making many small injections of microspheres along the way.

The magnification angiograms of the normal animals revealed in greater detail the obstruction produced by the microspheres (Plate 5a and 5b). The observations noted above were confirmed on the magnification angiograms.

The results of the blood flow studies in normal animals are presented in Table 3. Of the four normal extremities studied, three demonstrated definite reduction in flow after injection of the microspheres. In one extremity, there was actually a slight increase in flow after microsphere injection, the reason for the paradoxical finding could not be determined.

Most of the normal animals tolerated the injection of microspheres well and were in excellent condition at the time of follow up. Two animals that received high doses of microspheres, however, did show evidence of gangrene in the area injected, and one of these two dogs became paraplegic. Gangrene was encountered only when the dose of microspheres approached two grams, and was dependent on the number of microspheres injected, not the size. Autopsy of these animals revealed gross infarction of the muscles of the leg.

B. FISTULA ANIMALS

Inspection of an angiogram of the surgically created model of congenital arteriovenous fistula (Plate 1b) reveals many small tortuous vessels that feed the distal artery and veins, rather than the capillaries. That this lesion is analagous to human arteriovenous fistula can be confirmed by comparing Plate 1b to Plate 1a, which is an angiogram of a

human patient with this lesion. Both vascular beds allow rapid transfer of arterial blood to the venous system.

The features of the abnormal vasculature in the fistula animals can be more readily appreciated in the magnification angiogram. Comparison of angiograms in fistula animals before and after injections of microspheres (Plates 6a and 6b) demonstrates definite occlusion of the enlarged arterial branches. The 590-840 micron microspheres were found to be the most effective in occluding these enlarged channels, and in a few cases this size microsphere could be identified on the Bucky angiograms. One interesting phenomenon, occurring only in the fistula animals, is the retrograde filling of the artery distal to the fistula. This retrograde flow has previously been described by Holman (22), and it can be observed in these fistula animals.

From the results of the blood flow studies in Table 3, it can be seen that the flow is much greater in a fistulous than a normal extremity. Injection of microspheres reduces the flow. The amount of reduction in flow appears to be dependent on the dose of microspheres injected, as for the normal animals. Injecting many smaller branches individually results in greater obstruction in the fistula animals as well as the normal ones.

The results of the oxygen saturation studies are presented in Table 4. The venous oxygen saturations are high, as is expected in arteriovenous fistula, but unfortunately we do not have studies in the normal extremities. If the microspheres occluded a large part of the fistulous oxygen

rich arterial supply to the veins, the venous oxygen saturation would be expected to drop. If the venous oxygen saturations before and after injection in Table 4 are compared, it can be seen that no significant drop in venous saturation occurred. This is probably to be explained by the fact that with the very high arterial flow through the fistula vessels, the remaining arteriovenous shunts carried such a quantity of oxygenated blood that the drop expected in the venous saturation was effectively masked. Brown (5) has emphasized that he has found oxygen saturation studies in congenital arteriovenous fistula to be unreliable.

The fistula animals were found to tolerate poorly the procedures performed. Three of these animals died in the immediate post-operative period: two from acute blood loss after leak of the fistula, and one from an unknown cause. Three other animals died within twenty-four hours following angiography. After this, all fistula animals were digitalized before angiography, and all these animals survived. One animal was given a transfusion of 300 ml. of fresh dog blood. There was no gangrene in the fistula animals.

C. MICROSPHERE TRAP EXPERIMENT

In the animal into whose leg veins microspheres were injected directly, microspheres were found in the polyethylene trap in the inferior vena cava. Microspheres were not found in the traps of the four animals with a normal circulation which were injected via the arterial catheter. No

microspheres were trapped in the animal with a fistula injected with microspheres of a size calculated to occlude the enlarged collateral vessels. The effect of the microspheres on the lung, should they reach there, would probably not be very serious. McCaughan (42) injected 750 mg. of microspheres of 150-450 microns in diameter into the femoral veins of six dogs. He noted no immediate effect on the pulmonary circulation and when the animals were sacrificed three days later he found multiple small petechiae with small areas of hemorrhagic infarction in the lungs. He considered these changes to be of minimal to moderate severity, and he believed that they could easily be tolerated by a patient.

SUMMARY AND CONCLUSIONS

1. The feasibility of treating congenital arteriovenous fistulas by injection of microspheres was investigated by injecting the lower extremities of normal animals and of animals in which an arteriovenous fistula was surgically created. Ligation of the artery just proximal to the fistula caused the development of profuse collateral circulation as described by Holman. The gross characteristics of this collateral network are similar to those seen in congenital arteriovenous fistulas.

2. In normal animals, the microspheres occlude arterial flow, as shown by angiograms and by blood flow studies made before and after injection of the microspheres.

3. In animals with surgically created arteriovenous fistula, the intraarterial injection of microspheres occluded many of the tortuous vessels. Blood flow studies demonstrated a decrease in flow after injection of microspheres, but oxygen saturation studies revealed no decrease in venous saturation.

4. Microspheres injected intraarterially did not pass from arteries to veins in animals with a normal extremity or in animals with an arteriovenous fistula.

5. The intraarterial injection of microspheres in patients with congenital arteriovenous fistula is a promising method of therapy for such lesions and merits further investigation and refinement.

Table 1

Summary of Dogs

Normal Animals

Number	Dose and Size Microsphere	X-Ray Studies
4717	1.55 grams 250-350 microns	Schonander
4693	1.50 grams 250-350 microns	Schonander
4709	1.50 grams 250-350 microns	Schonander
4765	2.10 grams 88-125 microns	Schonander
4718	1.70 grams 28-53 microns	Schonander
4888	.375 grams 28-53 microns	Schonander
5332	1.0 grams 250-350 microns (R) 1.5 grams 250-350 microns (L)	Schonander and Flow Studies
5350	.75 grams 88-125 microns (R) 1.25 grams 88-125 microns (L)	Schonander and Flow Studies
5329	40 shot(R) 120 shot(L)	Bucky
5333	40 shot (R) 1.0 grams 250-350 microns (L)	Magnification
5367	1.0 grams 28-53 microns (R) 2.0 grams 28-53 microns (L)	Bucky
4890	2.0 grams 250-350 microns (R) 2.0 grams 250-350 microns (L)	Magnification
5316	No microspheres injected-animal expired.	

Table 1 (Continued)

Fistula Animals

Number	Dose and Size Microsphere	X-Ray and Other Studies
4685	0.5 grams 250-350 microns (R) 30 shot (R)	Schonander and Bucky
4720	0.5 grams 250-350 microns (R) 2.0 grams 590-840 microns (R)	Magnification and Bucky Films Blood Gases
4695	1.0 grams 590-840 microns (R)	Magnification and Bucky Films Blood Flow and Blood Gas Studies
4773	0.5 grams 590-840 microns (R) 1.0 grams 250-350 microns (R)	Magnification and Bucky Films Blood Gas Studies
4705	0.5 grams 88-125 microns (R)	Schonander
4769	1.0 grams 590-840 microns (R)	Magnification and Bucky Films
4679	Died two weeks post surgery-rupture of fistula.	
4712	Death five weeks post surgery-cause unknown.	
4721	Death one day post-surgery with large hematoma of right hind extremity. Probably cause of death-hypovolemic shock.	

Table 1 (Continued)

Microsphere Trap Animals

Number	Dose and Size Microsphere Injected	Result
A1-20-66	2.0 grams 28-53 microns injected into leg veins bilaterally. (Positive control)	Microspheres trapped
A1-13-66	2.0 grams 28-53 microns injected via arterial catheter bilaterally.	No microspheres trapped
A1-17-66	2.0 grams 28-53 microns injected via arterial catheter bilaterally.	No microspheres trapped
A12-20-65	2.0 grams 28-53 microns injected via arterial catheter bilaterally.	No microspheres trapped
A1-10-66	2.0 grams 28-53 microns injected via arterial catheter bilaterally.	No microspheres trapped
4711 (Fistula Animal)	2.0 grams 590-840 microns injected into right femoral artery via catheter	No microspheres trapped

Table 2

Characteristics of Microspheres

A. Glass Microspheres

Source: Microbeads Division
Cataphote Corporation
Jackson 5, Mississippi

Sizes:	Catalog Number
590-840 microns	203
250-35- microns	456
88-125 microns	1217
28-53 microns	2740

Specifications:
Manufactured from high-grade optical crown glass, with silica content not less than sixty per cent.
Guaranteed ninety per cent in size range specified.
Index of Refraction 1.50-1.55.
Hardness Mohs scale 6
Specific Gravity 1.45-1.55.

B. Metal Shot Number 12 "Lubaloy" Steel Shot

Source: Winchester-Western Division
Olin Mathieson Chemical Corporation
New Haven, Connecticut

Size:

Number 12 Shot 0.15 inches in diameter, 1170 microns.
2385 shot per ounce, 79.5 shot per gram.

Table 3

Blood Flow Studies

Number	Settings		Average of 3 readings	Flow ml./min.
5332 (Normal)	Gain 999 Gain Multiplier 4	Phase 190 Magnetic Field 2	(Right) Before Microspheres 34	117
			After 1.0 grams 250-350 microns 23	88
	Gain 999 Gain Multiplier 4	Phase 162 Magnetic Field 2	(Left) Before Microsphered 20	106
			After 1.5 grams 250-350 microns 34	111
5350 (Normal)	Gain 999 Gain Multiplier 2	Phase 202 Magnetic Field 3	(Right) Before Microspheres 23	160
			After 750 mg. 88-125 microns 13	99
	Gain 999 Gain Multiplier 2	Phase 190 Magnetic Field 3	(Left) Before Microspheres 10	92
			After 1.25 grams 88-125 microns 7	16
4695 (Fistula)	Gain 999 Gain Multiplier 2	Phase 195 Magnetic Field 1	(Right) Before Microspheres 91	1103
			After 1.0 grams 590-840 microns 62	753

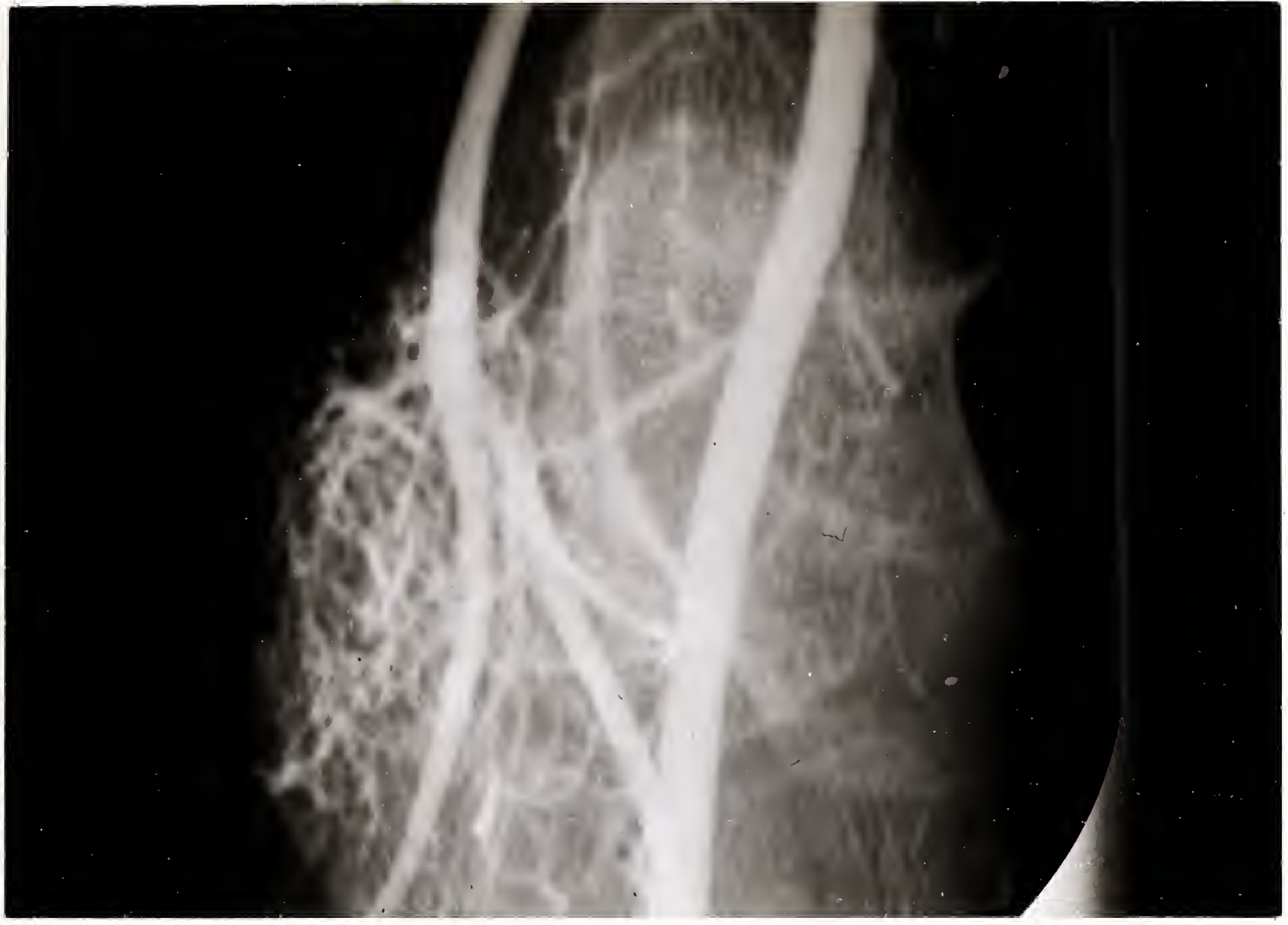
Table 4

Results of Blood Gas Studies

	Per Cent Saturation	
Number	Before Microspheres	After Microspheres
4773 (Fistula)	Arterial PO_2 83 92.6%	Arterial PO_2 63 85.0%
	Venous PO_2 72 89.3%	Venous PO_2 64 86.2%
4720 (Fistula)	Arterial PO_2 88 95.1%	Arterial PO_2 98 95.0%
	Venous PO_2 80 94.4%	Venous PO_2 87 93.0%
4695 (Fistula)	Arterial PO_2 75 92.7%	Arterial PO_2 84 95.8%
	Venous PO_2 66 90.0%	Venous PO_2 78 94.7%

Plate 1a. YNHH 41-09-42. Magnification angiogram of congenital arteriovenous fistula in leg of a young girl.

Plate 1b. Dog 4773. Magnification angiogram of fistula animal, showing tortuous, dilated vessels.



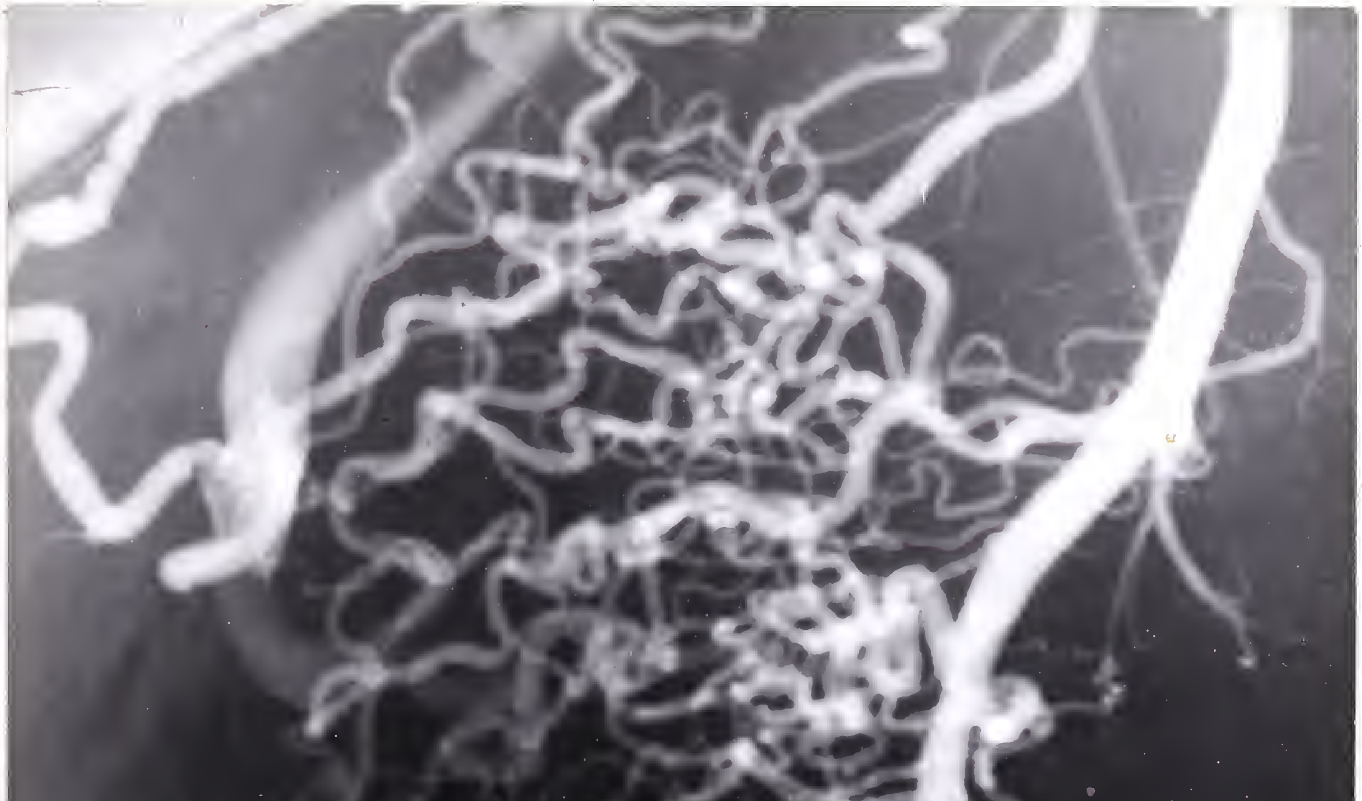


Plate 2

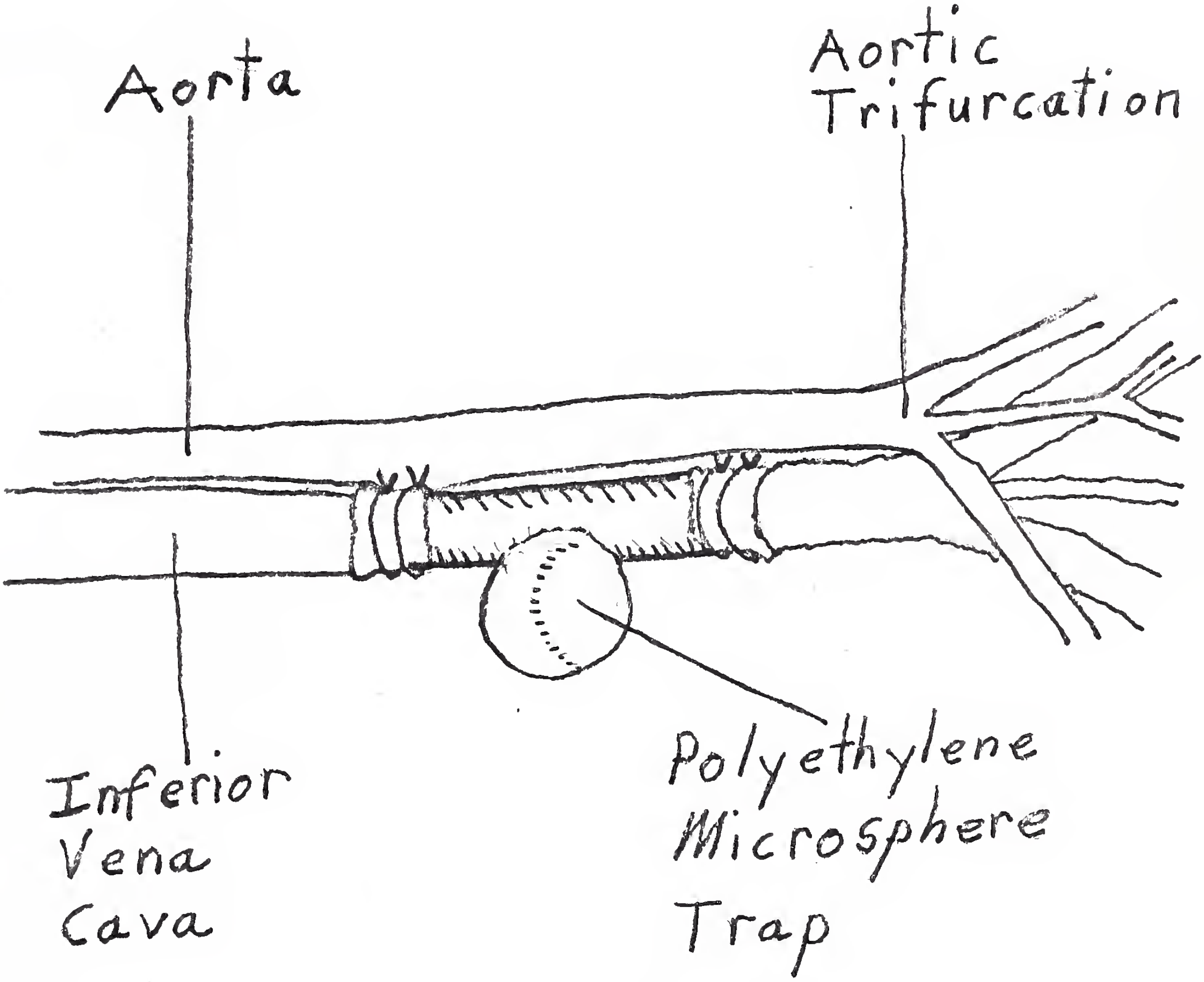

Aorta
Aortic Trifurcation
Inferior Vena Cava
Polyethylene Microsphere Trap

Plate 3a. Dog 4718. Normal angiogram before injection. Schonander film two seconds after injection.

Plate 3b. Dog 4718. Angiogram after 1.7 grams of 28-53 micron microspheres. Schonander film two seconds after injection. Note obstruction and retardation of flow.

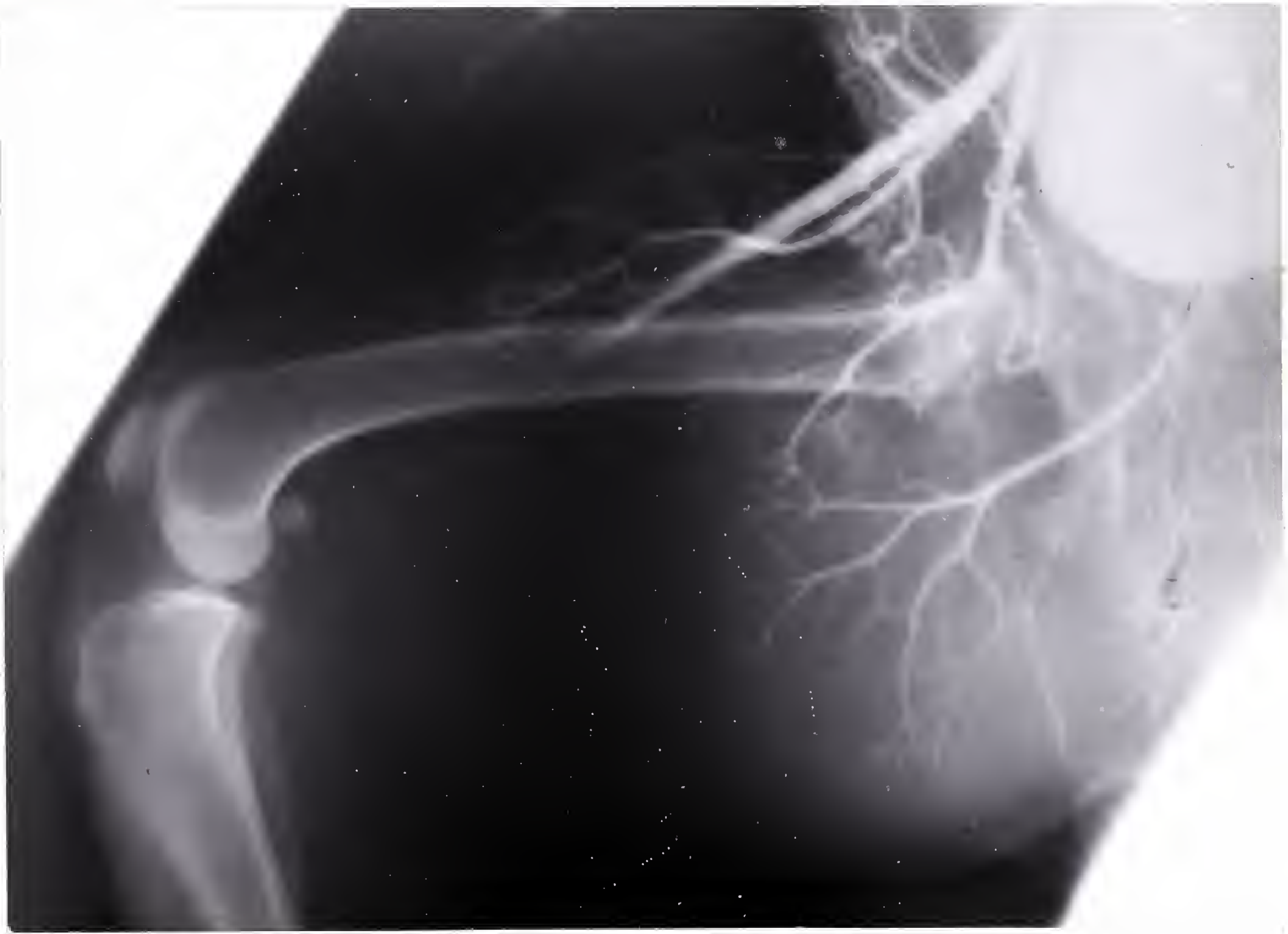


Plate 4. Dog 5329. Bucky film showing distribution of metallic shot injected through intraarterial catheter.

Plate 5a. Dog A2-14-66. Magnification angiogram of normal extremity before injection. Magnification approximately 2.5X.

Plate 5b. Dog A2-14-66. Magnification angiogram of normal extremity after injection of 2.0 grams of 250-350 micron microspheres. Note major obstruction of small vessels in this area. Magnification approximately 2.5X.

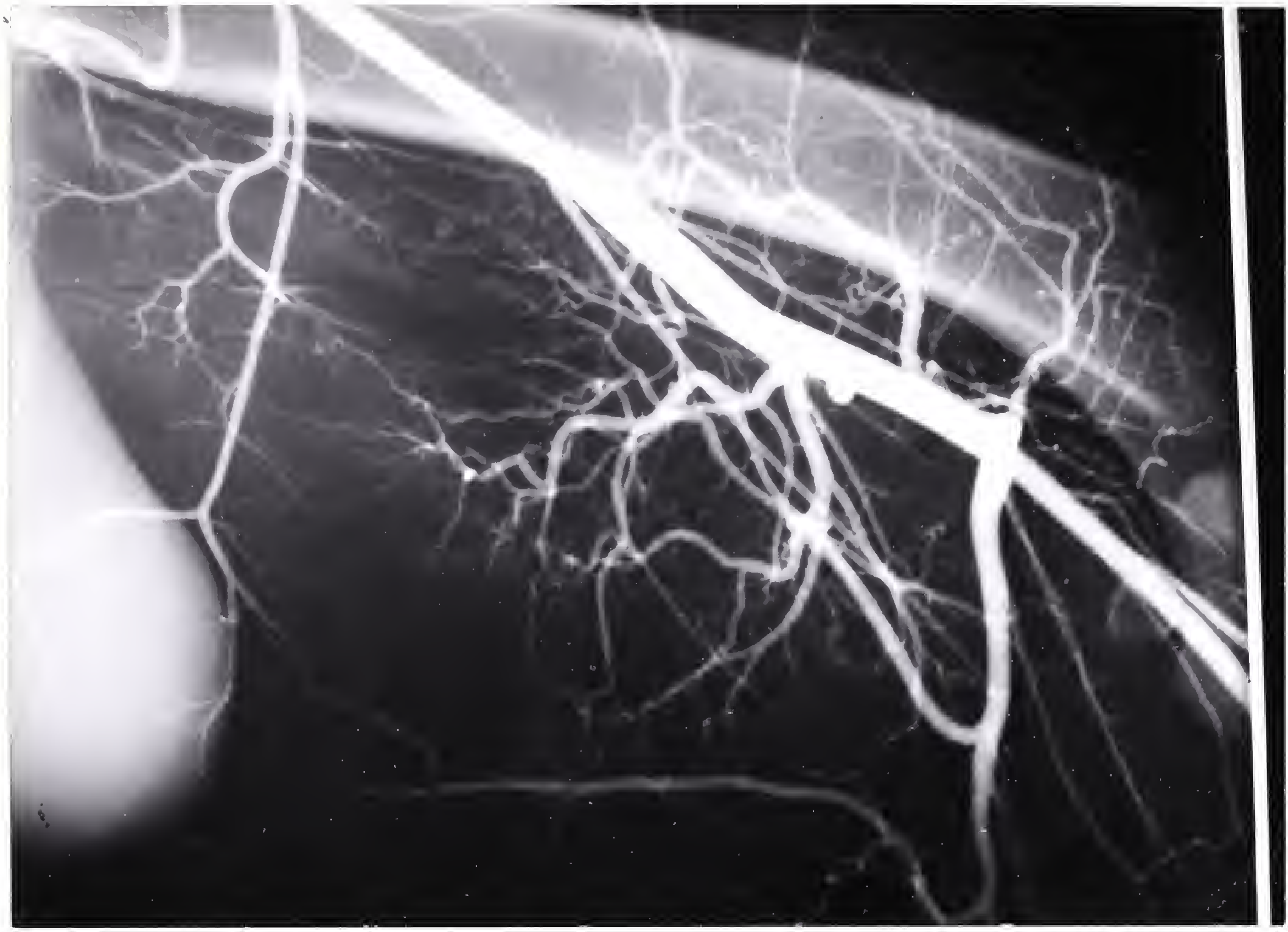
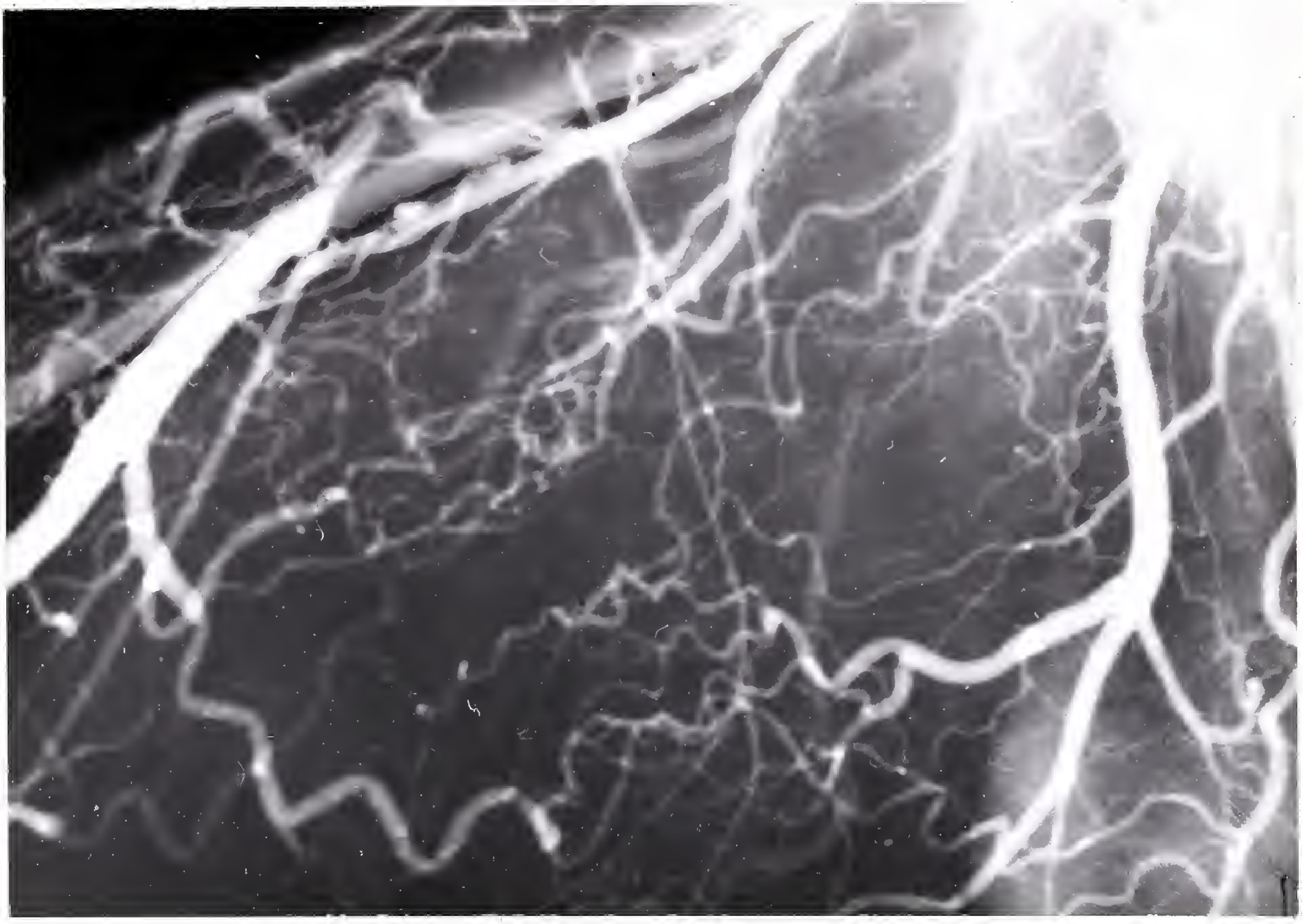
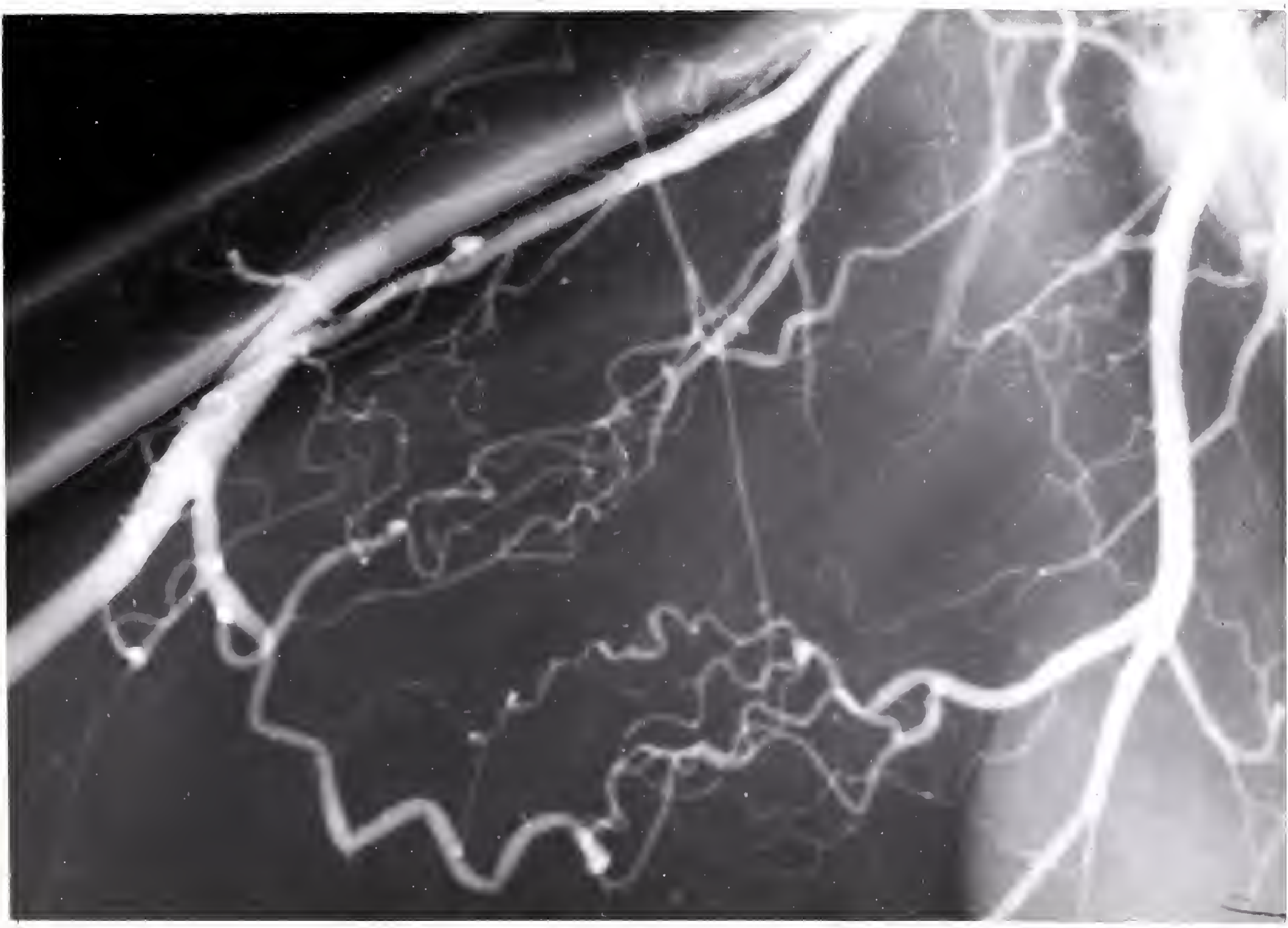


Plate 6a. Dog 4769. Magnification angiogram of fistula animal before microspheres. Magnification approximately 2.5X.

Plate 6b. Dog 4769. Magnification angiogram of fistula animal after 1.0 gram of 590-840 micron microspheres. Note definite obstruction of small, abnormal vessels. Magnification approximately 2.5X.





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